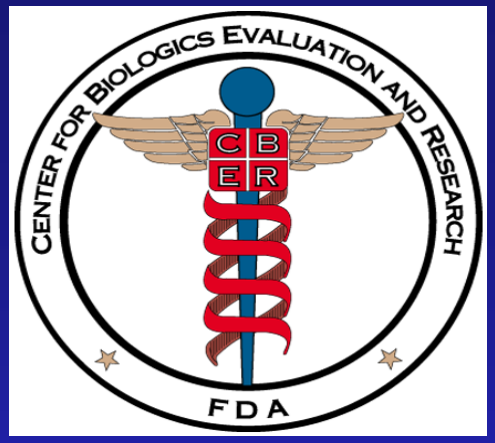

Quality Control Testing of Leukocyte Reduced Blood Components

Sharyn Orton, Ph.D.
OBRR/CBER/FDA

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Regulation

21 CFR 211.160(b) Laboratory Controls states:

"Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity."

Recommendation

Memoranda “Recommendations and Licensure Requirements for Leukocyte-Reduced Blood Products, May 29, 1996” recommends QC testing:

- Be performed using a sampling plan that includes 1% of monthly production; 4 per month for establishments producing < 400 units per month.

Acceptance Criteria

- Whole Blood/Red Blood Cells: residual WBC count of < 5.0 x 10e6; 85% retention of original product
- Platelets (from Whole Blood): < 8.3 x 10e5 per container; 85% retention of unpooled product
- Platelets, Pheresis: < 5.0 x 10e6 per container (device clearance by collection)
  - If by filtration, 85% retention of original product

continued

- Labeling of components as Leukocytes Reduced based on above criteria

The Question has been asked…..

Should FDA continue with the same monthly testing paradigm to monitor for non-conformance?

We believe it is appropriate to consider other scientifically and statistically sound QC plans.

One example is the use of scan statistics.

Non-conformance

- Noncomformance rates are generally expected to be low
  - Est. $<10^{-2}$ for manual/procedure
  - Est. $<10^{-3}$ for automated procedure
  - Failures may be clustered
- Power to detect non-conformance will probably be low for small sample sizes
- Some biologic variables (usually donor-related) cannot be controlled by current technology (e.g. HgbS-related failure)

Scan Statistics

One statistical method under consideration is the use of scan statistics. Scan statistics:

- Assess events that cluster in time and space (or are non-random)
- Use a rolling window of test results for non-conformance assessment

continued

Calculate the number of test failures required to trigger investigation of an unacceptable level of non-conformance by considering:

- an estimated non-conformance rate (0.1% for automated methods)
- $\geq$ 80% power to detect a failure rate of 5%
- an acceptable FP rate (< 5%)
- total % of collections to be tested (10%)

continued

QC monitoring will be assessed on a rolling basis

- All failures should be evaluated and corrected for attributable causes
- Non-process control failures are not counted

Example

Let's say that 24,000 Platelets, Pheresis are collected per year at your blood center.

- Test ~2,400 per year
- Random selection from total collections
- For this example, calculations use a "window" of 120 tests
  - 3 failures in the 120 test "window" would trigger an investigation of an unacceptable level of non-conformance
  - The false positive rate would be 4%

How Does This Work?

- For this example, let's say you perform 10 tests on any given day
- Start the rolling sample window of 120 tests.
  - As long as you have < 3 failures, the level of non-conformance for the process is considered to be acceptable.
  - After 120 tests are complete, the window "rolls" forward and the next 120 tests now include the testing of the samples from days 2-12, and a new set of 10 samples; those tested on the 13th day.

continued

First 120

Test day	1	2	3	4	5	6
Tests (cum)	10	20	30	40	50	60
Failures	0	0	0	1	0	0

Test day	7	8	9	10	11	12
Tests (cum)	70	80	90	100	110	120
Failures	0	0	1	0	0	0

√

continued

Second 120

Test day	2	3	4	5	6	7	
Tests (cum)	10	20	30	40	50	60	
Failures	0	0	1	0	0	0	
Test day	8	9	10	11	12	13	
Tests (cum)	70	80	90	100	110	120	**X**
Failures	0	1	0	0	0	1	

continued

- In the event of QC failure (trigger reached) a complete failure investigation should be initiated
- Corrective action and follow-up should be performed:
  - If resolved, QC should be re-initiated
    - The count of tests restarts at 0 (or day 1)
  - If not resolved, revalidation performed as appropriate

Examples of Sample Size

N	Window	Trigger	FP%	Power %
400	60	2	2	82
600	“	“	3	“
1200	120	3	0.7	95
2400	“	“	1.4	“
3600	“	“	2	“
4800	“	“	3	“

References

Glaz J, Naus J, Wallenstein S. Scan Statistics 2001. Springer Publishing.

Lachenbruch PA, Foulkes MA, Williams, AE, Epstein JS. Potential use of the scan statistic in the quality control of blood products J Pharm Statistics 15:353-366, 2005